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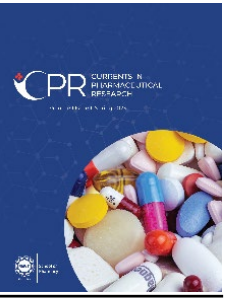

Title:	**Enhancement of Indomethacin Dissolution by Co-milling with Polyvinylpyrrolidone using Planetary Ball Milling**
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Enhancement of Indomethacin Dissolution by Co-milling with Polyvinylpyrrolidone using Planetary Ball Milling

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ABSTRACT

Indomethacin, a Biopharmaceutics Classification System II drug, is characterized by poor aqueous solubility. The purpose of this study is to evaluate the possibility of co-milling indomethacin with polyvinylpyrrolidone (PVP) by using planetary ball milling to enhance the apparent solubility and dissolution rate of indomethacin. For this purpose, different drug-to-polymer ratios were used, such as 1:1, 1:2, 1:3, and 1:4 of indomethacin to PVP, with 1 and 8 hours of milling time. The co-milled formulations were evaluated for bulk density, tapped density, angle of repose, Hausner's ratio, compressibility index, apparent solubility, *in vitro* dissolution, particle size, and crystallinity. Differences in drug-release behavior were observed among the co-milled formulations and pure indomethacin in their dissolution profiles. Powder X-ray diffraction revealed that the intensity of diffraction peaks decreased after co-milling, indicating that the amount of crystallinity can be reduced. The results indicate that co-milling with PVP using planetary ball milling is suitable for improving the dissolution and solubility profile of indomethacin.

Keywords: co-milling, indomethacin, polyvinylpyrrolidone, solubility enhancement

1 INTRODUCTION

Poor aqueous solubility is a major challenge in pharmaceutical formulation development because it can reduce the rate of drug dissolution and, in some instances, it can also reduce the bioavailability of the drug when given orally [1]. Indomethacin belongs to the non-steroidal anti-inflammatory group of drugs known as Biopharmaceutics Classification System class II (BCS class II) drugs. It is poorly water-soluble and exhibits polymorphic properties, which can affect its dissolution and

physicochemical properties [2]. A number of formulation strategies, such as nanocrystal preparation and solid dispersion, have been explored to enhance the dissolution characteristics of poorly water-soluble drugs [3]. For this purpose, a mechano-chemical process called co-milling is used, in which a drug is co-milled with an excipient or a polymer. This process can change the physical nature of the particles (such as their size and solid-state properties) and thus enhance the dissolution of the drug [4]. NQM-04 planetary ball mill is used for milling indomethacin and PVP. The particle size and solid state properties of the product change following co-milling and affect its dissolution performance [5]**.**

The polymeric carrier selected was polyvinylpyrrolidone (PVP). PVP is hydrophilic and extensively used in formulations aimed to enhance the dissolution of poorly water-soluble drugs. A potential basis for drug–polymer association in indomethacin-containing systems is reportedly the interactions between the carboxylic acid group of indomethacin and the carbonyl groups of PVP [6]. The latter is widely employed in the pharmaceutical industry as an aid to the dissolution of poorly water-soluble drugs. In the case of co-milled formulations, physical state of the drug changes and/or drug–polymer interactions may contribute to the performance of the formulation [7–10]. Due to its versatile nature, it has a wide variety of applications, such as tissue engineering, drug delivery systems, and ophthalmologic applications [12].

The aim of this study is to enhance the solubility of indomethacin for better pharmacological effects and improved bioavailability. Various formulations of indomethacin and PVP in different proportions and at different milling rates were prepared and characterized in terms of bulk density, tap density, angle of repose, Hausner's ratio, compressibility index, crystallinity, drug release profile, and solubility.

2 MATERIALS AND METHODS

2.1 Materials

Indomethacin was received as a gift sample from Munawar Pharmaceuticals (PVT) Ltd. While, PVP, HCl, methanol, potassium dihydrogen phosphate, podium hydroxide, and citric acid were purchased from Merck Pakistan.

In this study, indomethacin is the targeted drug whose solubility is to be enhanced for better pharmacological outcomes. PVP

(polyvinylpyrrolidone) is the polymer used to enhance the solubility of indomethacin. Whereas, HCl, methanol, potassium dihydrogen phosphate, potassium hydroxide, and citric acid were used for the preparation of phosphate buffer to analyze the solubility and dissolution profile of indomethacin.

2.2. Preparation of Co-Milled Formulations

Indomethacin was co-milled with PVP (on room temperature) using a planetary ball mill (NQM-04 planetary ball mill, China). The mill consists of a rotating turntable having four 50 mL SS cylinders. The containers of the ball mill were thoroughly cleaned, dried, and kept in desiccators; then they were loaded with (~2g) of different ratios of powder mixture containing indomethacin and PVP. The ratios of indomethacin and PVP used were 1:1, 1:2, 1:3, and 1:4. The powder to ball ratio was 1:10, made with 81 small zirconium balls of 0.6 cm diameter. Furthermore, 7 large zirconium balls of 1 cm diameter were added to the milling cylinders to fill each cylinder with ~30% of full capacity. The containers were closed tightly and rotated at 25 Hz. The samples were collected after 1 hour and 8 hours respectively and stored in moisture-resistant containers until used for characterization. Solubility, bulk characteristics, flow properties, dissolution, and PXRD studies were performed. Table 1 shows the codes and ratios for all the formulations.

Table 1. Ratios and Codes for The Co-Milled Samples of Solid Dispersion using PVP as Polymer in The Planetary Ball Mill

Formulation Code	Drug Polymer Ratio Indomethacin: PVP	Time of Milling (Hour)
F1	1:1	1
F2	1:2	1
F3	1:3	1
F4	1:4	1
F5	1:1	8
F6	1:2	8
F7	1:3	8
F8	1:4	8

2.3. Solubility Studies

The apparent solubility of pure indomethacin and co-milled

formulations of indomethacin–PVP were determined (in triplicate *n*=3) by the shake-flask method. An excess of about 20 mg of drug or formulation was added to a 100 mL conical flask that contained 20 mL of phosphate buffer (pH 7.4) at 25°C. The flasks were covered with an aluminum foil and agitated using a shaker at 50 rpm. The samples were taken at 2, 4, 6, 24, and 48 h, filtered through Millipore filter paper and diluted as necessary. The absorbance of the resultant solutions was measured on a UV spectrophotometer at 319 nm. A calibration curve was prepared in phosphate buffer (pH 7.4) in the range of 5 – 50 µg/mL and used to determine the concentrations.

2.4. *In vitro* Dissolution Study

Pure indomethacin and co-milled formulations were subjected to an *in vitro* dissolution study using USP Apparatus II (paddle method, Curio, Pakistan). Dissolution test was performed with the phosphate buffer solution (pH 7.4) at 37 ± 0.5 °C, with a paddle rotation speed of 50 rpm and using 900 mL of phosphate buffer solution. The experimental record indicated that 150 mg of pure indomethacin or the same amount of the co-milled formulation were introduced in each vessel. Samples were taken at specific time intervals, filtered, and then absorbance was measured with a UV spectrophotometer at 319 nm. After each withdrawal, a new and equal amount of fresh dissolution medium was added to keep the dissolution volume constant. A calibration curve was constructed in phosphate buffer (pH 7.4) within the reported range of drug concentrations (5-50 µg/mL) and used to calculate the concentration of indomethacin. Dissolution experiments were conducted in triplicate (*n* =3) and the average values of results were reported in the study.

3. RESULTS AND DISCUSSION

The apparent solubility measured in the shake-flask study showed that the indomethacin–PVP co-milled formulations had a higher apparent solubility than pure indomethacin under the experimental conditions. Solubility increased by increasing the milling time for co-milled samples. Pure indomethacin has a solubility of 0.4 mg/mL, whereas F6 shows 5mg/mL solubility value. These findings are in line with co-crystallization studies demonstrating how interactions like hydrogen bonds between the drug and co-former significantly increase solubility [11].

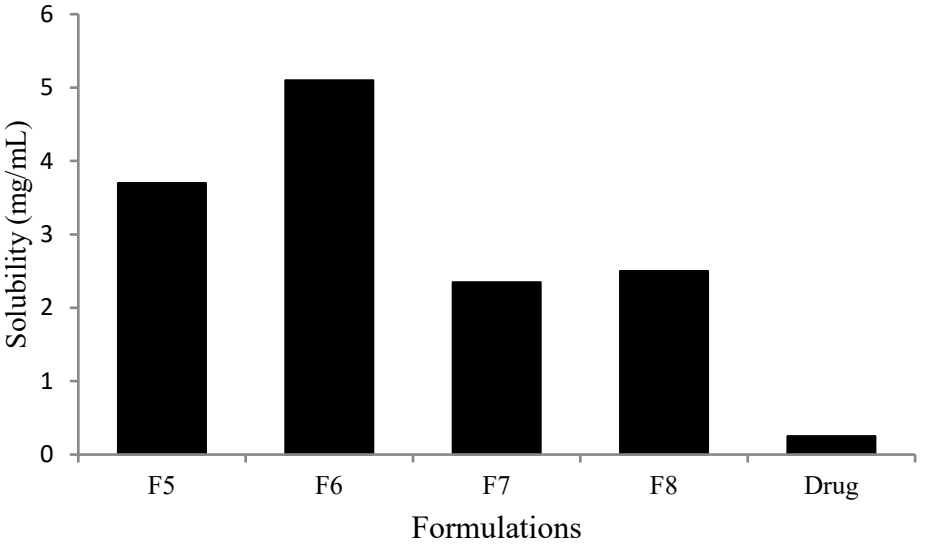

Figure 1. Solubility of Indomethacin and 8 hr co-milled Samples in mg/mL

Table 2. Data for Tapped Density, Bulk Density, Compressibility Index, and Hausner's Ratio

Sample	Bulk Density (g/mL)	Tapped Density (g/mL)	% Compressibility Index	Hausner's Ratio
Indo	2.76	3.32	16	1.2
F1	0.42	0.52	20	1.25
F2	0.42	0.55	24	1.33
F3	0.46	0.57	19	1.24
F4	0.48	0.59	18	1.21
F5	0.97	1.11	12	1.13
F6	0.72	0.83	13	1.15
F7	0.83	0.92	10	1.11
F8	0.83	1.66	50	2.0

The bulk and tapped density, compressibility index, and Hausner's ratio of indomethacin and co-milled formulations are shown below in Table 2. Compressibility indices and Hausner's ratios of F5, F6, and F7 show that they have good flow characteristics. While, F8 has a high compressibility index 0.50 (or 50%) and Hausner's ratio of 2.00, indicating very poor flow

characteristics. The values of flow properties obtained were interpreted on the basis of the powder-flow classification criteria, as stated in United States Pharmacopeia General Chapter <1174> Powder Flow.

For the 8 h co-milled formulations, Table 3 shows particle size values of 98.00, 110.25, 98.00, and 122.50 µm for the formulations F5, F6, F7, and F8, respectively. The particle size of F5 and F7 is the smallest, while that of F8 is the largest among these formulations. The current particle size data does not show any monotonic change with increasing PVP concentration.

Table 3. Ocular Micrometer Readings and Estimated Particle Sizes of the 8 h co-milled Formulations

Sample	Reading on the ocular scale	Particle size (µm)
F5	4.0	98.00
F6	4.5	110.25
F7	4.0	98.00
F8	5.0	122.50

Figure 2 compares the dissolution profiles of pure indomethacin and the eight-hour co-milled indomethacin–PVP formulations (F5–F8). The profiles show the differences in the drug-release behavior among the formulations. F6 showed a rapid increase in cumulative drug release, reaching approximately 80% at 30 minutes and 95% at 60 minutes. F7 reached its maximum release of approximately 95% at 40 minutes, followed by a decline and subsequent increase. F5 showed a gradual increase in drug release, reaching approximately 80% at 50–60 minutes. F8 exhibited a fluctuating profile, reaching approximately 75% at 50 minutes before decreasing to 60% at 60 minutes. In comparison, pure indomethacin reached approximately 82% cumulative drug release at 60 minutes. Overall, F6 demonstrated the highest cumulative drug release at the end of the test period, although F7 exhibited the highest release at 40 minutes.

The PXRD patterns exhibited lower intensities of the characteristic diffraction peaks following co-milling, indicating a decrease in the amount of crystallinity. However, these results are not an indication of full amorphization. The interactions between indomethacin and PVP also play a role in the dissolution behavior, although specific molecular interactions were not directly verified by the characterization techniques employed in this study [12].

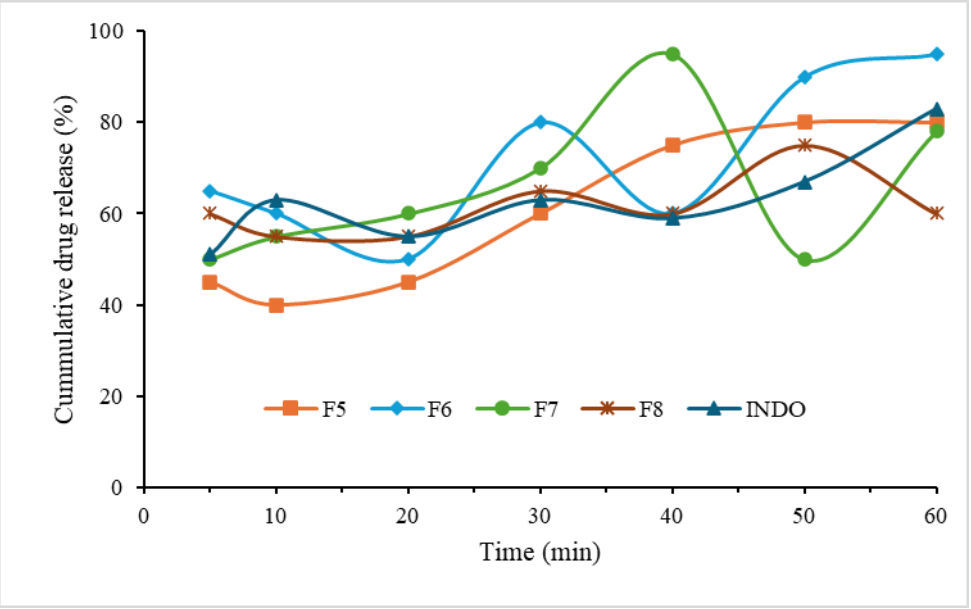

Figure 2. *In vitro* Dissolution Profiles of Pure Indomethacin and the Eight-hour Co-milled Indomethacin–PVP Formulations (F5–F8) in Phosphate Buffer (pH 7.4) using USP Apparatus II at 37 ± 0.5 °C and 100 rpm

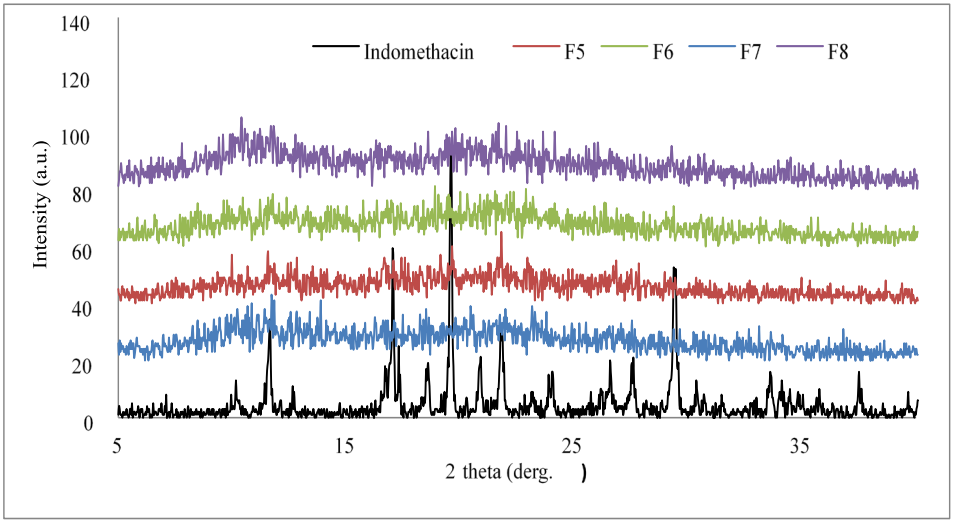

Figure 3. Powder X-ray Diffraction (PXRD) Patterns of Pure Indomethacin and the Eight-hour Co-milled Formulations F5, F6, F7, and F8, Showing Changes in the Diffraction Patterns Following Co-milling

The PXRD data also revealed reduction in the characteristic diffraction peaks in the co-milled formulations, which also indicated reduction in the crystalline order. The dissolution profile exhibited in the above mentioned solid-state changes may be attributed to these changes [13].

In general, it can be concluded that co-milling indomethacin with PVP may provide a better dissolution behavior under the tested conditions. These observed differences could be a result of changes in solid-state properties and any potential drug-polymer interactions, though the exact role of each factor could not be determined [14]. Additional studies with quantitative solid-state characterization, stability testing, and systematic formulation comparison would be useful to elucidate the dissolution differences observed [15].

3.1. Conclusion

The results indicate that by co-milling indomethacin with PVP, there may be an increased aqueous solubility and dissolution behavior. Changes in the PXRD patterns observed are in line with a decrease in the crystalline order of some co-milled formulations and could be related to the dissolution performance of these formulations.

3.2. Limitations

This study has some limitations including quantitative crystallinity analysis, particle size distribution measurements with modern techniques, and stability testing. In addition, further studies are required to determine the feasibility of scaling up the co-milling process along with *in vivo* bioavailability studies.

Author Contribution

Anam Ijlal: investigation, writing - original draft. **Amjad Hussain:** conceptualization, supervision. **Irfan Masood:** validation, visualization. **Muhammad Sohail Arshad:** writing – review & editing, formal analysis.

Conflict of Interest

The authors of the manuscript have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

Data Availability Statement

Data supporting the findings of this study will be made available by the corresponding author upon request.

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The authors did not use any type of generative artificial intelligence software for this research.

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